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SWITZER, JULIET CAROLINE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/816,357	LIEW, CHOONG-CHIN	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2007 and 30 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49,50,52,53 and 56-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49,50, and 58-76* is/are rejected.

7)☒ Claim(s) *52,53,56,57 and 77* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is written in response to the papers received 11/26/07 and 11/30/07. Any rejections which are withdrawn but not addressed have been overcome by amendment to the claims or cancellation of the rejected claims. This action is FINAL.

Claim Objections

2. Claims 52, 53, 56, 57, and 77 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiply dependent claim. These claims each are multiply dependent and depend themselves from multiply dependent claim 60. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 59, 60-65, 67, 68, 69, 71-75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 59 depends from itself and thus is an incomplete claim and is therefore rejected as indefinite. All claims which depend from claim 59 are also incomplete and indefinite. The dependent claims are all multiply dependent from claim 59 and have been considered in this office action insofar as they depend from one of the other alternatives. For example, claim 60 has been considered insofar is it depends from claim 58.

Claim Rejections - 35 USC § 112

6. Claims 50, 67, 68, and 69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a rejection for new matter.

7. In claims 50, 67, 68, and 69, the limitation that the blood samples "comprises leukocytes which a have not been fractionated into cell types" is new matter. Such a recitation includes, for example, testing a blood sample where the red blood cells and the white blood cells have been separated, and also includes, the testing of whole blood RNA. There is clearly basis for the latter, but not the former.

8. Applicant asserts in the remarks that this claim limitation finds clear support in the specification, including figure 5C which shows standardized fractions of leukocytes. However, these are not leukocytes that have not been fractionated into cell types, as they have clearly been fractionated into cell types. While RNA levels have been determined in each of the fractions, this is not basis for the negative limitation "have not been fractionated into cell types." There is no discussion or example in the specification of the testing of RNA in blood samples which comprise leukocytes which have not been fractionated into cell types. Applicant has attempted to present a claim which excludes a particular process step from a method (that is, fractionating the leukocytes) and then provides basis for the exclusion of the step in a method where the opposite occurred. This is not sufficient basis for the claim limitation because there is nothing in the specification that suggests applicant contemplated the exclusion of a step of fractionating

leukocytes into cell types. Therefore, claims 50, 67, 68, and 69, as well as all claims which depend from these claims are rejected for having new matter.

5. Claims 49, 50, 58, and 60-76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention

The invention of claim 49 is expressly drawn to a method detecting rheumatoid arthritis in a human test subject. The claims all include a step of quantifying a level or RNA encoded by a cell division cycle associated 1 (CDCA1) gene in a blood sample obtained from said human and comparing the level with a quantified level of RNA encoded by said gene in blood samples of control subjects which are classified as healthy control subjects, also comparing the test level with a quantified level of control RNA encoded by said gene in blood samples of control subjects which are classified as having rheumatoid arthritis and wherein said comparison of a statistically significant determination resulting from steps the comparisons that expression of said gene in said sample of said test subject is different relative to said samples of said control subjects classified as healthy control subjects, and is similar relative to said samples of said control subjects classified as having rheumatoid arthritis is indicative of rheumatoid arthritis in said human test subject.

Claim 58 is drawn to a method for detecting expression of a gene encoding a cell division cycle associated 1 (CDCA1) in a human "test subject." Claims which depend from claim 58 set

forth that the detected expression is quantified and compared to quantified level of control RNA encoded by said gene in blood samples of control subjects. Listed control subjects include healthy subjects and subjects that have rheumatoid arthritis. Further dependent claims set forth steps of classifying or identifying the test subject as being a candidate for having rheumatoid arthritis depending on the outcome of the comparing steps. Thus, it is clear that the intended use of claim 58 and those that depend from claim 58 is for classifying or identifying the test subject as being a candidate for having rheumatoid arthritis.

Claim 66 is drawn to a method of screening a human test subject "for being a candidate for having rheumatoid arthritis" and includes similar steps of detection of the CDCA1 gene in a blood sample, quantifying the expression and comparing the level to a quantified level of control RNA encoded by said gene in blood samples of control subjects classified as healthy subjects, where said test subject is a candidate for RA if said level of RNA encoded by said gene in said blood of said human is significantly different relative to that of said control subjects classified as healthy subjects with a p value of less than 0.05.

In claim 70, the invention is drawn to a method a method for classifying CDCA1 gene expression in a human, and sets forth steps of quantifying a level of RNA encoded by a CDCA1 gene in a test subject, comparing that level to a level of RNA found in blood samples from control subjects having rheumatoid arthritis and also comparing it to control subjects who are healthy. The independent claim states that based on particular determinations, the classification of CDCA1 gene expression results either with that of said subjects having rheumatoid arthritis or with that of subjects who are healthy.

The nature of the invention requires the knowledge of a reliable relationship between CDCA1 expression in blood and the presence of or indication of rheumatoid arthritis. Further, the practice of the invention requires an understanding of how the presence of rheumatoid arthritis effects the level of CDCA1 expression in human blood. The practice of the invention requires an understanding of how the presence of rheumatoid arthritis effects the level of CDCA1 expression in human blood in patients having rheumatoid arthritis versus patients that do not have rheumatoid arthritis but may have some other disorders. The nature of the invention requires the knowledge of a reliable association between CDCA1 expression and the ability to classify a particular individual's expression with the expression of subjects having rheumatoid arthritis or not having rheumatoid arthritis, and further, the use of this method requires that there is an underlying assumption that this classification is meaningful. Reading the claims in light of the specification it is clear that applicant intends to use such a classification method in order to provide a tool that is used as part of a diagnostic process, and such a use requires the knowledge of a reliable association underlying the classification.

Many of the claims additionally require a step of comparing the level of RNA detected in a test subject to "a quantified level of control RNA encoded by said gene in blood samples of control subjects." To practice these claims, it is essential to know the quantified level of control RNA encoded by said gene in blood samples of control subjects.

Scope of the claims

Many aspects of the claims remain quite broad.

In some claims the health status of the control individuals is entirely undefined, and encompass subjects with rheumatoid arthritis, cancer, healthy patients, patients with some other

disease, such as patients with a particular stage of rheumatoid arthritis, patients with rheumatoid arthritis in combination with other conditions, or patients with lupus etc. The claim which recite that the control subjects "do not have rheumatoid arthritis" remains quite broad given that this could encompass control subjects with any other possible disease, disorder or treatments.

The claims are very broad in scope because they encompass that ANY level and direction of difference in gene expression between the healthy controls or the controls not having rheumatoid arthritis is indicative of said rheumatoid arthritis, if that difference is "statistically significant." That is, the claims do not set forth that one level should be higher or lower than the other, and further do not set forth how much of a "difference" between two individuals would be necessary to draw the conclusions set forth in the claims. Most claims do not recite a level of statistical significance that is required to be reached, and so, the claims remain quite broad since no particular level is required, and the claims even encompass using different levels of statistical significance for different comparisons. The phrase "statistically significant" describes a mathematical measure of difference between groups, not a particular level of difference which is acceptable. There is no universally accepted level of "statistically significant."

Teachings in the Specification/Examples

Regarding rheumatoid arthritis, the specification provides example 20 wherein gene expression profiles of blood samples from individuals having rheumatoid arthritis were compared with normal individuals, that is healthy patients. The specification teaches that 2,068 genes were identified as being differentially expressed, and regarding the instant claims, table 3M provides a list of these genes (Example 20). CDCA1 is among the genes.

The table lists genes that were differentially expressed, but does not provide any further information. For example, the tables do not teach if the expression was higher or lower in rheumatoid arthritis patients versus controls.

The specification does not provide any guidance as to the level of "difference" that is sufficient (1 fold, 2 fold, etc) to result in a conclusion that rheumatoid arthritis is detected, nor does the specification provide any guidance as to the direction of the difference (higher or lower expression) that is expected to be observed for any single pairing of samples.

The specification fails to provide information about an essential aspect of the invention, namely, the nature of the difference in expression that was observed between rheumatoid arthritis patients and healthy patients. Furthermore, though the specification teaches that this gene is differentially expressed in rheumatoid arthritis patients versus healthy patients, the specification teaches this is true for thousands of genes. There is no guidance or analysis of data in the specification to suggest that this gene in particular, and considered in isolation, is sufficient to conclude that rheumatoid arthritis is present in a sample, as is instantly claimed. This information is essential to understanding and practicing the claimed invention because it is critical to knowing how to interpret a particular comparison result.

State of the Prior Art and Level of Unpredictability

The expression of genes the example was tested by hybridization of samples to a microarray that contains genetic information for tens of thousands of genes. This technology area is highly unpredictable, and as a result significant guidance is required to practice inventions using this type of data. Lee (Clinical Chemistry, 47:8, 1350-1352 (2001)) teaches that despite the technical accuracy of individual observations on an array, these data "are much more prone

to numerous false-positive findings fundamentally because of (a) an extremely large number of observations and (b) a very wide dynamic range of gene expression values obtained from gene chip experiments." In view of these unpredictable aspects of applying such data, Lee teaches that replication is necessary to begin to screen out false positive results. There is no replication in the instant specification.

Observing differences in expression between two populations is a highly unpredictable endeavor. For example, while the specification demonstrates that this gene was differentially expressed in the samples collected, the specification does not undertake analysis to see if this gene is differentially expressed in the blood of patients having other autoimmune diseases. Thus, if one were to detect expression of CDCA1 in blood that is different from healthy patients, it would be highly unpredictable if this difference is due to the presence of rheumatoid arthritis in particular or some other disease or condition. It is highly unpredictable how would one begin to know if that level of expression indicated rheumatoid arthritis, SLE, both, one but not the other, something in between or even some other condition or disorder for which the expression profile has not yet been determined.

Furthermore, although CDCA1 was not observed to be differentially expressed in any of the other examples in this specification, it is unknown and unpredictable whether it would be expressed in the blood of patients having other autoimmune diseases or any other diseases which were not tested in the instant specification or diseases which were tested in the instant specification but in a different population of test subjects, and whether this expression would be different from levels of expression in healthy controls. A method for detection which relies on a comparison between expression in the blood of a test subject and control subjects requires the

knowledge of this information in order to reliably "detect" rheumatoid arthritis, as set forth in the claims. The instant specification has not established that all difference, no matter the magnitude nor the direction, relative to any control subjects or even relative to a healthy control subject is indicative of rheumatoid arthritis. It is not known under what circumstances the result observed in the instantly examined control and test populations would be repeatable, as the results have not been validated. But even if one were to obtain the same result, it would be unknown because applicant did not disclose the magnitude of difference in expression between rheumatoid arthritis patients or controls, nor did applicant disclose the direction of variation. All of these inquiries are particularly important in this case since the specification is silent as to which differential expression observations would be sufficient to detect the presence of rheumatoid arthritis.

In the post-filing art, Osman et al. provide an analysis which includes microarray hybridization of test and control isolated from total cellular RNA where the test is patients with bladder cancer and the control is healthy individuals (Osman et al. Clinical Cancer Research 2006; 12(11) 3371-3380). Although Osman et al. are analyzing bladder cancer and not rheumatoid arthritis, they provide some cautionary guidance regarding their study which could equally and fairly be applied to the study provided to support the instantly claimed invention. Osman et al. teach that their study has several limitations including that "the expression profiles may represent the activation of specific immunologic response to the presence of bladder tumors, and that the profiles identified in this study may be intrinsic to the cohort of patients evaluated in this study (p. 3379)." The field remains highly unpredictable years after the filing of the instant application, even with the significantly more guidance given in this post-filing date reference.

Further, the claims of the instant application set forth the comparison of the gene expression in a single individual versus as few as two other individuals, and they set forth that a comparing gene expression between the two is "indicative of" rheumatoid arthritis. Neither the specification nor the claims set forth a threshold of difference between an individual's expression and the control expression of CDCA1 in the blood that would be sufficient to conclude that the difference in gene expression between a test individual and any type control group is "indicative of" any of the recited rheumatoid arthritis. Because the claims encompass any level of altered gene expression, it is relevant to point out that the art of Cheung et al (2003) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). It is thus unpredictable as to whether or not any level of altered gene expression is indicative of a rheumatoid arthritis or the absence of rheumatoid arthritis.

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the post-filing art of Wu (2001). Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The

conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion). The art of Newton et al (2001) further teaches the difficulty in applying gene expression results. Newton et al. teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph). There is no replication of data in the instant specification.

Quantity of Experimentation

The instant specification does not provide enabling support for the practice of a single embodiment within the claimed invention. In particular, the specification does not provide adequate guidance to appraise one of ordinary skill in the art as to what levels of CDCA1 gene expression must be observed to successfully conclude that rheumatoid arthritis is present. Further, although the specification teaches there are differences in CDCA1 levels in a rheumatoid arthritis population versus a control patient population, the specification is silent as to the nature of the "difference" in magnitude or direction. Thus, given the lack of teaching in the specification and the highly unpredictable nature of the technology, an extensive amount of work would be required to practice the claimed invention.

In order to practice the claimed invention, one would have to undertake an extensive amount of experimentation in a highly unpredictable technology area. One would begin by trying to reproduce the results observed in the instant specification to determine if there is a relative upregulation or downregulation of CDCA1 in rheumatoid arthritis patients versus healthy control patients, as the specification does not even provide this minimal guidance.

Without this knowledge one would not even begin to know how to interpret any results obtained in practicing the claimed methods. For example, consider the comparison of a test result and a control population of healthy individuals. How different from the average level of expression of healthy individuals would the test result have to be to indicate rheumatoid arthritis? Would any difference, up or down regulation be indicative of rheumatoid arthritis? Or could one indicate rheumatoid arthritis and one a different disease or condition, such as lupus? Is CDCA1 expressed differently in the blood of individuals with a disease other than lupus and rheumatoid arthritis relative to control populations? Is this expression also diagnostic of other autoimmune diseases or other or other disorders entirely unrelated to rheumatoid arthritis? In order to reliably use a method for detecting rheumatoid arthritis, one would first have to answer at least these questions. One would also, however, have to carry out this testing for validation, for it is possible that the result observed in the instant specification is intrinsic to the cohort of patients evaluated in applicant's study. Further, one would have to undertake experimentation to determine difference thresholds required to determine that a patient has or does not have a disease.

As discussed, this art area is highly unpredictable.

Conclusion

The claims include methods which encompass the detection in blood of the expression of CDCA1 in a test subject and comparing this expression to control subjects, wherein the comparison itself "is indicative of rheumatoid arthritis." The identification of gene differential expression/disease indication relationships is a highly unpredictable endeavor, requiring extensive experimentation. The specification provides minimal guidance. In light of the factors

discussed, therefore, it is concluded that it would require undue experimentation to practice the claimed invention.

Although some of claims are drawn to a method of "detecting expression" or "classifying expression," and not to diagnosis or identifying increased likelihood of disease or the like, it is critical to understand how the classification can be used in order use the claimed invention. In this case, the specification does not provide sufficient guidance as to how to use the detecting or classification methods other than in methods that are directed towards diagnostic purposes. What is the meaning of classifying expression "with that of subjects having" rheumatoid arthritis or with subjects who are healthy? While one could do the method steps as written, thus satisfying the "how to make" aspect of 112 1st paragraph, the specification does not provide sufficient disclosure to satisfy the how to use aspect of the requirement.

The data in the specification is not replicated. As discussed in the rejection, it is established that the technology on which the instant claims is based is a highly unpredictable technology, and in the face of such a high level of unpredictability, replication is necessary before results can be considered sufficient to support claims directed at classifying the gene expression of an individual test subject. Therefore, even this claim, after having considered all of the factors set forth in this rejection, lacks proper enablement.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 58, 60, 61, 62, 63, 67, 68, 69, 71, 72, 73, and 75, are rejected under 35 U.S.C. 102(a) and 102(b)as being anticipated by William Chittenden, dissertation submitted to the faculty of Virginia Polytechnic Institute and State University, August 2002.

8. These claims are not fully supported under 112 1st paragraph in the instant application nor any of the previously filed applications for at least the reasons discussed in this office action. This reference is applied under 102(a) and 102(b). If applicant establishes support for the claimed invention to a prior application such that the 102(a) and/or 102(b) does not apply the rejection will be withdrawn.

Chittenden teaches quantification and analysis of gene expression in mRNA isolated from whole blood, by isolating cells, precipitating RNA, producing cRNA and hybridization with the probe array HG-U133A, quantification of hybridization and calculation of differential expression. It is an inherent property of this array that it contains probes to CRSP6, and thus, the method taught by Chittenden is a method which uses an oligonucleotides of predetermined sequence which are specific for CRSP6. This chip also inherently has thereupon housekeeping genes that are used for quantifying expression. Further Chittenden tests individuals with disease and healthy controls (p. 58-59, 62-66). Chittenden does not specifically discuss CDCA1 expression, but it would have inherently been detected in the blood of healthy controls by the hybridization and array reading methods.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 58, 60, 61, 62, 63, 65, 67, 68, 69, 70, 71, 72, 73, and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maas et al. (The Journal of Immunology, July 1, 2002, Vol. 169, pages 5-9) in view of Affymetrix GeneChip Human Genome U133 Set datasheet, 2001.

Maas et al. teach a method for detecting the expression of genes in blood from individuals having rheumatoid arthritis and patients not having rheumatoid arthritis (healthy controls) which includes isolating total RNA from a whole blood sample, processing it, hybridizing it to a microarray, quantifying the expression and identifying differentially expressed genes. Maas et al. detected genes which were differentially expressed between patients having RA and healthy control patients, and classify gene expression as being with the patients who have rheumatoid arthritis or healthy controls based on the level of difference of expression observed between the two types of samples.

The content of the array (Research Genetic GF-211 membranes) used by Maas et al. was not available to the examiner at the time of writing this office action, but this array included probes to a number of different coding genes. This chip also inherently has thereupon housekeeping genes that are used for quantifying expression, and at the time the invention was made it was routine to detect gene expression relative to a housekeeping gene. It is unknown if CDCA1 was among those genes.

However, at the time the invention was made, Affymetrix had provided the GeneChip Human Genome U133 Set which included CDCA1 among the genes which are detected by the

array. It would have been prima facie obvious to one of ordinary skill in the art to have substituted the Affymetrix gene chip for the one used by Maas et al. Because both references teach arrays that are useful for detecting gene expression in a wide variety of genes, with the Affymetrix array providing means to detect over 38,000 transcripts, it would have been obvious to one of ordinary skill in the art to have substituted one array for another to achieve the predictable result of detecting the expression of many different genes in the blood of individuals having RA versus controls. Such a substitution would have inherently and necessarily resulted in the detection and quantification of CDCA1 in the blood samples of the patients having RA and the healthy control patients.

11. Claims 58, 59, 60, 61, 62, 63, 65, 67, 68, 69, 70, 71, 72, 73, and 75, are rejected under 35 U.S.C. 103(a) as being unpatentable over Heller et al. (PNAS USA Vol. 94, p. 2150, March 1997) in view of both Affymetrix GeneChip Human Genome U133 Set datasheet, 2001 and Sharma et al. (WO 98/49342; cited in IDS).

Heller et al. teach a method for detecting the expression of genes in a sample from individuals having rheumatoid arthritis and patients not having rheumatoid arthritis (healthy controls) which includes isolating total RNA from a the sample, processing it, hybridizing it to a microarray, quantifying the expression and identifying differentially expressed genes. Maas et al. detected genes which were differentially expressed between patients having RA and healthy control patients, and classify gene expression as being with the patients who have rheumatoid arthritis or healthy controls based on the level of difference of expression observed between the two types of samples.

Heller et al. do not teach the use of an array which includes probes for CRSP6.

However, at the time the invention was made, Affymetrix had provided the GeneChip Human Genome U133 Set which included CDCA1 among the genes which are detected by the array. This chip also inherently has thereupon housekeeping genes that are used for quantifying expression, and at the time the invention was made it was routine to detect gene expression relative to a housekeeping gene. It would have been prima facie obvious to one of ordinary skill in the art to have substituted the Affymetrix gene chip for the one used by Maas et al. Because both references teach arrays that are useful for detecting gene expression in a wide variety of genes, with the Affymetrix array providing means to detect over 38,000 transcripts, it would have been obvious to one of ordinary skill in the art to have substituted one array for another to achieve the predictable result of detecting the expression of many different genes in the blood of individuals having RA versus controls. Such a substitution would have inherently and necessarily resulted in the detection and quantification of CDCA1 in the blood samples of the patients having RA and the healthy control patients.

Heller et al. in view of the Affymetrix product sheet do not teach detecting applying their analysis to the gene expression in a blood sample, and in particular detecting CDCA1 in a blood sample.

Sharma et al. teach that from the very early stages of diseases the whole organism response to the changed condition (p. 10, 4th full ¶). In light of this, Sharma et al. teach a method for identifying a marker useful for diagnosing a disease comprising the steps of detecting the presence of RNA in an unfractionated sample of whole blood from each of one or more subjects having said disease and quantifying a level of said RNA in said sample. Namely, Sharma et al. teach the preparation of gene transcript patterns beginning with extraction of

mRNA from tissues, cells or body parts of an individual or organism which has a disease or condition (p. 7, final ¶, p. 12, 1st ¶), and particularly teach the isolation of mRNA from unfractionated whole blood samples, where unfractionated is interpreted as meaning that the cell types within blood were not separated from one another (p. 35, section 5.1.1). Sharma et al. teach quantifying the level of expression and determining a difference between the quantified level in the sample from the diseased subject and a similarly quantified level of genes of control RNA from an unfractionated sample of whole blood from each of one or more first control subjects (p. 5, step (d); p. 15, first full ¶; p. 18, step (f); p. 11, final ¶). Sharma et al. teach that these methods are carried out by producing amplification products from RNA extracted from an unfractionated sample of whole blood (p. 18 and p. 35, Example 5). Sharma et al. specifically suggest that this method can be applied to the study of schizophrenia (p 6, 3rd ¶).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Heller et al. in view of the Affymetrix product sheet so as to have additionally tested the blood of the patients having RA and the healthy control samples. One would have been so motivated by the express teachings of Sharma et al. that disease exerts a global effect on individuals and that this effect can be measured by gene expression in the blood. The identification of markers for disease in the blood suggests a potential minimally invasive method to detect this disorder. One would have been motivated to continue to use the microarray analysis taught by Heller et al. in view of the Affymetrix product sheet since the use of the microarray enables large scale screening of many different human genes, and Sharma et al. expressly teach that marker genes may be identified by

differential hybridization methods, which Heller et al. in view of the Affymetrix product sheet use (see Sharma, paragraph bridging pages 4-5).

Response to Remarks

Applicant traverses the rejection for lack of enablement. The claims were extensively amended, and the rejection has been amended to address the amended and newly filed claims. The remarks are addressed insofar as they remain relevant.

Applicant states on page 11 that the instant claims recite two clearly defined sets of controls; patients having RA and healthy controls. However, many of the claims are broader, with some not defining the controls and with some including any controls that "do not have rheumatoid arthritis."

Applicant states that the elected biomarker CDCA1 is enabled as an indicator of RA as described in the claims without disclosing the direction or level of difference that exists between patients having RA and individuals not having RA (p. 11-12). Applicant argues that the fact that the claims require determination of a statistically significant similarity between the test subject and control subjects having RA disease makes it unnecessary to include the direction and magnitude of the difference because no direction or magnitude information is required in order to compare for similarity, stating that the declaration exemplifies that it would not take undue experimentation to make the claimed comparisons. Applicants contend that it does not require undue experimentation for one of skill in to determine the inherent direction or level of the statistically significant differential expression required for the claimed methods of detecting a rheumatoid arthritis, given the widely established and validated analytical tools for analyzing gene expression, and so it is not necessary for applicant to have taught the exact direction or

level of difference between the two populations for one of skill to practice the invention (p. 12). However, the rejection is maintained, due to the highly unpredictable nature of this technology, as discussed in the rejection. The instant specification fails to provide a critical piece of information with regard to understanding the relationship between CDCA1 expression and RA. The specification invites one of skill in the art to undertake experimentation to (a) determine the relationship between RA and CDCA1 expression and then to validate that relationship. There is a fundamental absence of information given in the specification. The claims all set forth comparing the test level to "a quantified level of RNA encoded by said gene in blood samples from control subjects..." but the specification does not provide this quantified level, or any quantified level. So, it is left to one of skill in the art to establish what is critical for the practice of the invention. While the specification may rely on the state of the prior art to help enable the invention, the specification may not rely on the state of prior art to supplement what is critical to the practice of the invention- in this case the quantified levels of control RNA encoded by the gene in the control subjects, no matter which type of control subjects.

Applicant argues that the differential expression of CDCA1 as between subjects having RA and not having RA is predictable, since a statistically significant difference was found. This does not remove the fact that the nature of the difference was not disclosed (and that nature is entirely unpredictable) and that the finding was not replicated. Also, the specification teaches that this same gene is also differentially expressed in healthy patients compared to those having lupus, but there is no means or guidance as to how to differentiate the expression of CDCA1 in the blood of "test subjects" such that one might begin to know which autoimmune disease is present, or if both are present.

Applicant disagrees with the contention based on Wu et al. that expression data needs to be interpreted in view of other biological knowledge (page 13). Wu was relied upon for much more than this simple statement. Wu discusses at length many of the factors that make gene expression analysis unpredictable. Applicant's statement that "differential gene expression which is reproducible, and is correlated with the state of health or disease of the individual does not necessarily result directly in the state of the disease of the individual" is attorney argument which is not supported by evidence on the record. Even if the changes are a result of downstream effects of the pathogenic process, they are related to the state of disease in the individual. Applicant points out that certain prostate markers were used as biomarkers without an understanding of their function. The examiner is not trying to require an understanding of CDCA1 in RA or any other disease, nor does Wu suggest that such is necessary. The examiner is looking to the specification for adequate guidance for making and using an invention in a highly unpredictable field of endeavor.

Applicant states that the results of Cheung et al. cannot be reliably extrapolated to primary blood samples since Cheung et al. are using cultured cell lines. However, this is irrelevant to the point of Cheung et al. which is that among individuals (in this case cell lines) there is natural variability in gene expression for any particular gene. Attorney arguments are not sufficient to establish that this biological fact is not the case.

Applicant suggests that extending the findings of the instant application to larger samples is merely routine. However, in the absence of the critical disclosure of the specification and the unpredictable nature of the technology, the further experimentation is inventive- applicant has

provided one of skill in the art with an invitation to discover the actual relationship between CDCA1 expression in the blood and RA.

The instant situation differs tremendously from In re Angstadt, wherein a large number (forty) examples were provided, only one of which did not work. In In re Angstadt, the court determined that there was sufficient guidance in an unpredictable art. The court further stated, however, that "each case must be determined by its own facts." The facts of this case do not support an enabled use for the claims, for all of the reasons discussed in the rejection. Here, the situation is quite different because the specification does not provide data or guidance sufficient to support the claims of any embodiment of the claimed invention, let alone multiple embodiments.

Applicant further argued in supplemental arguments filed 11/30/07 Pascual et al. teach that CDCA1 is upregulated in SLE patients who are likely to progress to renal involvement relative to SLE patients which are not likely to progress. The comments specifically referring to Pascual et al. have been removed. The examiner regrets the confusion caused by the error. Applicant provides further argument relating to the fact that Pascual et al. detected expression in PMBC, asserting that their claims exclude such analysis. However, this is not persuasive since the claims are all inclusive of embodiments "wherein the sample is whole blood" and are all drawn using "comprising" language which is permissive of additional steps such as taking a whole blood sample and then fractionating it. No claim positively recites that the detection and quantification takes place in RNA samples that contain total blood RNA as applicant appears to be trying to argue.

Conclusion

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Wednesday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is

(571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

February 28, 2008